REMARKS

Claims 1, 11, 13-23, 25-33, 37-42 and 53 are pending in this application. Claims 43-52 are withdrawn from consideration to a non-elected status. Claims 1, 11, 13-23, 25-33, 42 and 53 were variously rejected under 35 U.S.C. § 112, first paragraph. Claims 1, 11, 13-23, 25-33, and 37-42 were variously rejected under 35 U.S.C. § 103.

By this amendment, claims 11 and 53 have been cancelled, claim 1 has been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendment can be found, *inter alia*, throughout the specification, for example, in originally filed claim 11 and in Example 1.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1, 11, 13-23, 25-33, 42 and 53 were rejected under 35 U.S.C. §112, first paragraph, as allegedly because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

The claimed invention is directed to modulating an immune response to a second antigen through co-administration of (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and (ii) a second antigen.

In the rejection of claims 1, 13-23, 25-33, 42 and 53, the Examiner states that the specification is enabling for methods for modulating a Th1 immune response "by co-administering the second antigen with an ISS-antigen complex," but not for "modulating a Th-1 response to a second antigen that is co-administered with the ISS-antigen complex at a different site of administration from the ISS-antigen complex." Office Action, page 2.

Applicants respectfully disagree with this assertion for reasons already of record in this application. Applicants again point out that the experimental results in the specification demonstrate that co-administration of the ISS-antigen complex and β-gal at two different sites results in an increased Th1 response to the β-gal. This notwithstanding, solely in the interest of expediting prosecution, the claims have herein been amended to recite that the complex and the second antigen are co-administered at the same site.

The Examiner rejected claims 1, 11, 13-23, 25-30, 32, 33, 37-42 and 53 alleging that the specification does not provide enablement for immunostimulatory sequences that are shorter or do not conform to SEQ ID NO:1. Applicants respectfully traverse this ground for rejection.

The claimed invention is directed to use of a complex in which an ISS-containing polynucleotide is covalently conjugated to an antigen. In the invention, the administration of the complex modulates the immune response to a co-administered second antigen.

Applicants respectfully submit that the specification provides all the information required for one of skill in the art to make and use the invention to modulate the immune response

to the second antigen as claimed. The specification teaches the requirements for the ISS and the immunomodulatory polynucleotide of the complex and provides methods by which ISS can be made and evaluated for immunomodulatory activity. See, for example, page 15, line 30, to page 21, line 17. The specification describes antigens and how to make the polynucleotide-antigen complexes for use in the invention. See, for example, page 21, line 20, to page 32, line 19. The specification provides guidance for the administration and formulations for administration of the claimed compositions. See, for example, page 39, line 30, to page 47, line 8. Finally, the specification provides methods to assess the modulation of the immune response as claimed.

Accordingly, the specification teaches how to make and use the claimed invention without undue experimentation. Applicants respectfully submit that a *prima facie* case for lack of enablement has not been established.

The Examiner cited the teaching of Fearon[1] in support of this rejection. Applicants respectfully disagree with the characterization of the teaching of Fearon in the Office Action and that the teaching of Fearon supports the enablement rejection.

Fearon presents data for the immunostimulatory activity of ISS-containing oligonucleotides used alone ("free ISS") and from ISS-containing oligonucleotides in cPLGA complexes ("ISS-cPLGA"), both of which differ from ISS-antigen complex of the instant invention. Certainly, the activity of the free ISS used in Fearon is not an appropriate standard of comparison for the activity of the ISS composition of the claimed invention. The ISS-cPLGA complexes of Fearon are also different from the complexes of the present invention, although ISS-cPLGA complexes are arguably more similar to the ISS-antigen complexes of the instant invention than is free ISS. As can be seen in Fearon, an ISS can have very different activities when presented alone

[1] Fearon et al. (2003) European Journal of Immunology 33:2114-2122; "Fearon."

("free") and when in the cPLGA formulation. See, for example, the activity of TCGTCGA in Fig. 2. When complexed with cPLGA, even quite short ISS molecules have significantly more activity than free ISS (see, for example, TCGTT and TCGTC in Fig. 2). Thus, Applicants respectfully submit that the teachings of Fearon regarding the ISS sequence requirements for activity are not appropriate to support a lack of enablement in the present invention since Fearon teaches compositions other than those claimed. Be that as it may, the following discussion is to address the points made in the rejection.

The Examiner points to the inactivity of the sequence ACGTTCG in support of the enablement rejection and concludes that it would require undue experimentation to make and use the invention commensurate with the scope of the claims. Indeed, Fig. 2 of Fearon indicates that ACGTTCG, either as free oligonucleotide or in a cPLGA complex, was found to have no immunostimulatory activity as tested. However, Fearon demonstrates many other CG containing oligonucleotides of varying length and sequence with immunostimulatory activity. See, for example, Fig. 2 and Fig. 3.

The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. M.P.E.P. §2164.08(b); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). Applicants respectfully submit that, as outlined above, the specification provides ample teaching by which the skilled artisan can test a particular oligonucleotide for immunomodulatory activity as claimed. "The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Still further, the Examiner points to the first paragraph of the discussion and states that "Fearon et al. also teach that a consensus ISS motif has been recognized in murine models, the equivalent human motif has not yet been identified." Office Action, page 5. Applicants respectfully submit that the cited paragraph of Fearon describes identifying sequences flanking the CG dinucleotide that result in **optimal** activity of the ISS. Indeed, Fearon appears focused on optimization of the sequences with greatest immunostimulatory activity in the context of cPLGA complexes. For example, although Fearon describes that a minimal sequence length for potent stimulation of IFN is 5 bases, oligonucleotides with only 3 and 4 bases stimulated much more IFN than media or oligonucleotides without CG (Fig. 2). Thus, the entirety of Fearon appears to be directed to the optimization and refinement of immunostimulatory sequence activity as opposed to identifying sequences with some, if not optimal, activity.

For a *prima facie* case on non-enablement, the burden is on the Office to demonstrate that there is a reasonable basis to question the presumptively sufficient disclosure made by applicant. See, for example, In re Wright, 27 USPQ2d 1510 (Fed. Cir. 1993). Applicants respectfully submit that the Examiner has not produced adequate evidence to support a lack of enablement, i.e., to establish that with the teachings in the specification, a person skilled in the art could not determine an ISS-containing immunomodulatory polynucleotide comprising a CG sequence that, when covalently conjugated to a first antigen, can modulate an immune response to a co-administered second antigen.

Applicants respectfully submit that the pending claims are in compliance with the enablement requirements.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §103

Claims 1, 11, 13, 14, 17, 20-23, 25-33, 37 and 40-42 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Schwartz *et al.* (WO 98/55495, "Schwartz") or Carson *et al.* (WO 98/16247, "Carson"), as further evidenced by Horner *et al.* (*Cellular Immunology,* November, 1998; 190:77-82, "Horner") or Chu *et al.* (*J. Exp. Med.* 1997; 186(10):1623-1631, "Chu"). Claims 15 and 38 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson further evidenced by Horner or Chu and further in view of Lee et al. (*Ann. Med.* 30:460-468 (1998), "Lee"). Claims 16 and 39 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson further evidenced by Horner or Chu and further in view of Durali et al. (*J. of Virol.* 72(5):3547-3553 (1998), "Durali"). Claims 18 and 19 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson further evidenced by Horner or Chu and further in view of Anderson (US Patent No. 4,673,574). Applicants respectfully traverse these rejections.

A *prima facie* case of obviousness requires that three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143. If any one of these three

criteria is not met, a *prima facie* case of obviousness has not been established. As presented below, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

The amended claims are directed to a method of modulating an immune response to a second antigen through co-administration of (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and (ii) a second antigen, where the amount of the complex administered is sufficient to modulate an immune response to the second antigen. The claimed invention is also directed to a composition comprising (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a viral conserved polypeptide (first antigen) and (ii) a viral variable polypeptide (second antigen) and to a composition comprising (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to an allergen (first antigen) and (ii) a second antigen.

Claims 1, 4, 6, 11, 13-14, 17, 20-23, 25-33, 37 and 40-42 over Schwartz or Carson, as further evidenced by Horner or Chu.

The present invention is based on the observed benefit of co-administration of an ISS-first antigen complex with a second antigen in the modulation of the immune response to the second antigen. As demonstrated in this application, administration of an ISS-first antigen complex with a second antigen results in an enhanced T_h1 immune response to the second antigen as compared to a T_h1 response that would be obtained upon administration of the second antigen with the ISS in an admixture and as compared to the immune response to the administration of the second antigen without an ISS.

Both Schwartz and Carson describe immunomodulatory activity of an ISS-antigen conjugate composition and immunomodulatory activity of an ISS + antigen admixture. Nothing in Schwartz or Carson teaches or suggests that the modulation of an immune response to a free

(unconjugated) antigen would be greater if the free antigen was administered with an ISS-antigen complex[2] instead of with a free ISS. Further, one skilled in the art would have no expectation of success of the claimed invention from the teaching of Carson or Schwartz.

In the Office Action dated June 2, 2003, the Examiner acknowledges that Schwartz and Carson do "not explicitly teach administering a second antigen with the [ISS-antigen] composition." June 2, 2003 Office Action, pages 9 and 12. Applicants further submit that a skilled artisan would not be motivated to do so from the teachings of Schwartz or Carson.

The Examiner concedes that that described at lines 1-2 on page 5 of Schwartz is ambiguous.[3] Further, Applicants respectfully disagree with the Examiner's characterization of Schwartz at page 12, lines 9-15 on page 6 of the Office Action. More of the sentence quoted from Schwartz at page 12, lines 9-15, on page 6 of the Office Action is as follows: "...ISS can be administered in conjunction with one or more members of the group of immunomodulatory molecules comprising antigens ... and/or immunomodulatory facilitators ... and adjuvants... ." The plain reading of this statement would be a disclosure of administration of ISS alone, ISS + antigen, ISS + facilitator, ISS + adjuvant, ISS + antigen + facilitator, ISS + antigen + adjuvant, ISS + facilitator + adjuvant, and ISS + antigen + facilitator + adjuvant; but *not* ISS + multiple antigens. Thus, contrary to what appears in the Office Action, Schwartz is not specifically suggesting that ISS be administered with more than one antigen, but rather with one or more members of the group of immunomodulatory molecules, of which group antigens are but one example.

This plain reading of Schwartz is confirmed and reinforced by Schwartz at page 12, lines 29-31 ("The ISS and **the** antigen **and/or** immunomodulatory facilitator can be administered

[2] Where the two antigen are different, as claimed.
[3] See page 6 of the March 9, 2004 Office Action.

together in the form of a conjugate... ," emphasis added) and at page 14, lines 8-14 ("The ISS and **the** antigen can be administered as an ISS-antigen conjugate... ," emphasis added). These citations clearly state that the ISS is administered with only one antigen. Further, these last two quoted passages of Schwartz are the only ones in Schwartz that discuss conjugation, and in each case they talk about a single antigen, with no mention of additional antigens, conjugated or unconjugated. So the notion that Schwartz, anywhere, suggests administering an ISS-first antigen conjugate along with an unconjugated second antigen is one wholly unsupported by the document itself.

Both Horner and Chu describe the generation of a T_h1 immune response to an antigen as a result of administration of an admixture of an ISS-containing oligonucleotide and the antigen. However, neither reference teaches or suggests the coadministration of an ISS-first antigen conjugate complex with a second antigen nor provides any motivation to do so.

With regard to Carson, the Examiner states that "[o]ne of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Carson teaches that antigens administered **with an ISS conjugate** elicit a T_h1 immune response." Office Action, page 7, emphasis added. Applicants respectfully point out that Carson teaches that ISS-antigen administered **as a conjugate complex** (not *with a conjugate*) elicits a stronger immune response than ISS + antigen administered. See, for example, Carson, page 10, lines 3-11. As it was known in the art that ISS + unconjugated antigen elicits a T_h1 immune response (see, for example, Horner or Chu), the ISS-antigen conjugate complex must therefore elicit a stronger T_h1 immune response than the unconjugated co-administration of ISS + antigen. Carson does not teach or suggest that this stronger Th1 response provided by conjugation transfers in any way to a second, unconjugated antigen.

If one were to assert that cited references suggest administration of a second antigen with an ISS-first antigen complex (which Applicants decidedly do not), knowledge in the art would **at most** suggest to the skilled artisan that co-administration of an ISS-first antigen complex and a second antigen would result in an immune response akin to that from administration of an admixture of the ISS and the second antigen.

Nothing in these references, or in the art, suggests that the benefit of conjugation to an ISS would be extended to a second, but unconjugated, antigen. Thus, the cited references do not provide an expectation of success of the claimed invention, i.e., a stimulation of an enhanced Th1 immune response to a second antigen when it is co-administered with an ISS-first antigen conjugate complex.

Applicants respectfully submit that a *prima facie* case of obvious has not been made. Thus, Applicants respectfully submit that the claimed invention is not obvious in view of either Schwartz or Carson, further evidenced by Horner or Chu.

Even if it was argued that a *prima facie* case is made (which it decidedly is not), Applicants respectfully point out that the claimed method and composition results in an unexpected and very different response than any predicted response that would flow from the teachings of Schwartz or Carson. As presented in Dr. Van Nest's Declaration,[4] co-administration of a second antigen with the ISS-first antigen complex resulted in an unexpectedly greater immune response to the second antigen than that observed with administration of the antigen and an uncomplexed ISS in an admixture. Data presented in the specification and in the Van Nest Declaration also indicate a greater suppression of a T_h2 response to the second antigen with co-administration of a second

[4] See Dr. Van Nest's Declaration, submitted October 23, 2002.

antigen with the complex. Thus, Applicants respectfully point out that the claimed methods and compositions of the present invention produced results well beyond expectation.

Again, Applicants respectfully submit that the claimed invention is not obvious in view of either Schwartz or Carson, further evidenced by Horner or Chu.

Claim 15 and 38 over Schwartz or Carson, as further evidenced by Horner or Chu, and further in view of Lee.

Claims 15 and 38 are directed to a method and a composition of the invention in which the first antigen is influenza nucleocapsid protein. As outlined above, the claimed invention is not obvious over Schwartz or Carson. Lee describes that ISS within DNA vaccines result in a Th1 immune response to the encoded antigen and describes the use of DNA vaccines encoding influenza proteins in tests for infection protection.

Lee does not supply what is missing from the primary reference, Schwartz or Carson, as further evidenced by Horner or Chu, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen. None of the references, either alone or in combination, describes or suggests the composition as claimed. Nothing in the references, or in the art, suggests that the benefit of conjugation to an ISS would be extended to the second, but unconjugated, antigen. Thus, the cited references do not provide an expectation of success of the claimed invention, i.e., a stimulation of an enhanced Th1

immune response to a second antigen when it is co-administered with an ISS-first antigen conjugate complex.

Claims 16 and 39 over Schwartz or Carson, as further evidenced by Horner or Chu, and further in view of Durali.

Claims 16 and 39 are directed to a method and a composition of the invention in which the first antigen is HIV gag protein. As outlined above, the claimed invention is not obvious over Schwartz or Carson. Durali describes production of cytotoxic T lymphocytes against HIV antigens from various HIV clades.

Durali does not supply what is missing from the primary reference, Schwartz or Carson, as further evidenced by Horner or Chu, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen. None of the references, either alone or in combination, describes or suggests the composition as claimed. Nothing in the references, or in the art, suggests that the benefit of conjugation to an ISS would be extended to the second, but unconjugated, antigen. Thus, the cited references do not provide an expectation of success of the claimed invention, i.e., a stimulation of an enhanced Th1 immune response to a second antigen when it is co-administered with an ISS-first antigen conjugate complex.

Claims 18 and 19 over Schwartz or Carson, as further evidenced by Horner or Chu, and further in view of Anderson.

Claim 18 is directed to a method of the invention in which the first antigen is diphtheria toxin mutant (CRM197). Claim 19 is directed to a method of the invention in which the first antigen is diphtheria toxoid. As outlined above, the claimed invention is not obvious over Schwartz or Carson. Anderson describes diphtheria toxoid and diphtheria CRM 197 as carriers in vaccine preparations.

Anderson does not supply what is missing from the primary reference, Schwartz or Carson, as further evidenced by Horner or Chu, and the combinations of Schwartz or Carson and the secondary references do not teach or suggest the claimed invention, thus do not render the claimed invention obvious.

None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen. None of the references, either alone or in combination, describes or suggests the composition as claimed. Nothing in the references, or in the art, suggests that the benefit of conjugation to an ISS would be extended to the second, but unconjugated, antigen. Thus, the cited references do not provide an expectation of success of the claimed invention, i.e., a stimulation of an enhanced Th1 immune response to a second antigen when it is co-administered with an ISS-first antigen conjugate complex.

In sum, Applicant respectfully submit that a *prima facie* case of obviousness has not been made. Thus, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

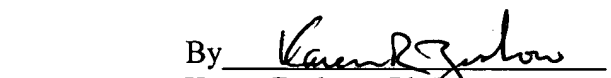
CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882000800.

Dated: June 9, 2004

Respectfully submitted,

By 

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